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Epidermolysis Bullosa Acquisita Develops in Dominant Dystrophic Epidermolysis Bullosa

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TO THE EDITOR

Dystrophic epidermolysis bullosa (DEB) is a congenital inherited blistering disorder caused by mutations in *COL7A1*, the gene encoding collagen VII (COL7), which is a major structural component of anchoring fibrils of the hemidesmosome. COL7 protein comprises a central triple helical domain flanked by a 145 kDa noncollagenous amino-terminal domain (NC1) and a 30 kDa carboxyl-terminal domain (Burgeson, 1993). DEB shows either autosomal dominant (DDEB; OMIM#131750) or recessive (RDEB; OMIM#226600) inheritance (Fine et al., 2014). In contrast, epidermolysis bullosa acquista (EBA) is a chronic, autoimmune, subepidermal blistering skin disease with circulating IgG antibodies against COL7 (Kim and Kim, 2013). In skin of patients with EBA, linear deposition of IgG and C3 along the dermal-epidermal junction (DEJ) is evident with direct immunofluorescence; additionally, indirect immunofluorescence with patient sera shows linear deposition of IgG along the dermal side of the DEJ on 1 M NaCl split skin of normal control individuals. In most cases of EBA, epitopes of the auto-antibodies are within the NC1 domain of COL7 (Lapiere et al., 1993). Interestingly, anti-COL7 antibodies can be generated in patients with RDEB (Pendaries et al., 2010; Tampoia et al., 2013; Woodley et al., 2014), or DEB pruriginosa, which is an allelic disorder of DDEB (OMIM#604129) (Jedlickova et al., 2012). Besides these findings, whether DEB and EBA can coexist in a single individual is largely unknown. Here, we describe a rare case of DDEB complicated by EBA.

We have seen a three-generation Japanese family with DDEB at Niigata University Hospital (Figure 1a). All three affected individuals in the family showed blister formations on their hands and feet during early childhood, whereas other skin areas and oral mucosa were unaffected. The skin symptoms improved with aging and resulted in scar formation and dystrophic nails (Figure 1b–d). After obtaining institutional approval of experiments and written informed consent from the patients, we performed direct sequencing analysis and identified a recurrent heterozygous missense mutation c.7868G>A (p.Gly2623Asp) in the *COL7A1* gene of all three affected individuals (Supplementary Materials and Methods online) (Figure 1e). On the basis of previous reports of DDEB with the identical mutation (Varki et al., 2007) or other missense mutations at the amino acid position 2623 (Christiano et al., 1995; Sawamura et al., 2006; Varki et al., 2007), we expected a good prognosis for the affected individuals in this family.

To our surprise, however, the eldest patient in the family (I-1; Figure 1a) eventually showed bullae and subsequent scar formation all over her body, including oral mucosa at the age of 63 (Figure 1f–h). Skin biopsy from her left arm revealed subepidermal bulla formation with dense infiltration of lymphocytes, eosinophils, and neutrophils (Figure 1i). Although circulating autoantibodies against the NC16a domain of 180 kDa bullous pemphigoid antigen were not evident in blood test, we postulated that she might suffer from an autoimmune blistering disease. To test this hypothesis, we conducted a series of analyses with samples of this patient's skin and serum (Supplementary Materials and Methods). Direct immunofluorescence with skin sections from this patient revealed linear deposition of IgG and C3 at the DEJ (Figure 1j; data not shown). In addition, indirect immunofluorescence with 1 M NaCl split normal human skin sections and the patient's serum clearly demonstrated linear deposition of IgG at the dermal side of the DEJ (Figure 1k), suggesting that the antigen recognized by the auto-antibodies localized below the lamina lucida. Strikingly, Western blot analysis with the patient's serum showed a 290 kDa fragment in dermal extracts from a control individual, which corresponded to the molecular weight of COL7 (Figure 2a). By contrast, the patient's serum did not recognize any component of laminin

Abbreviations: COL7, collagen VII; DDEB, dominant dystrophic epidermolysis bullosa; DEB, dystrophic epidermolysis bullosa; DEJ, dermal-epidermal junction; EBA, epidermolysis bullosa acquisita; NC1, noncollagenous amino-terminal domain; RDEB, recessive dystrophic epidermolysis bullosa

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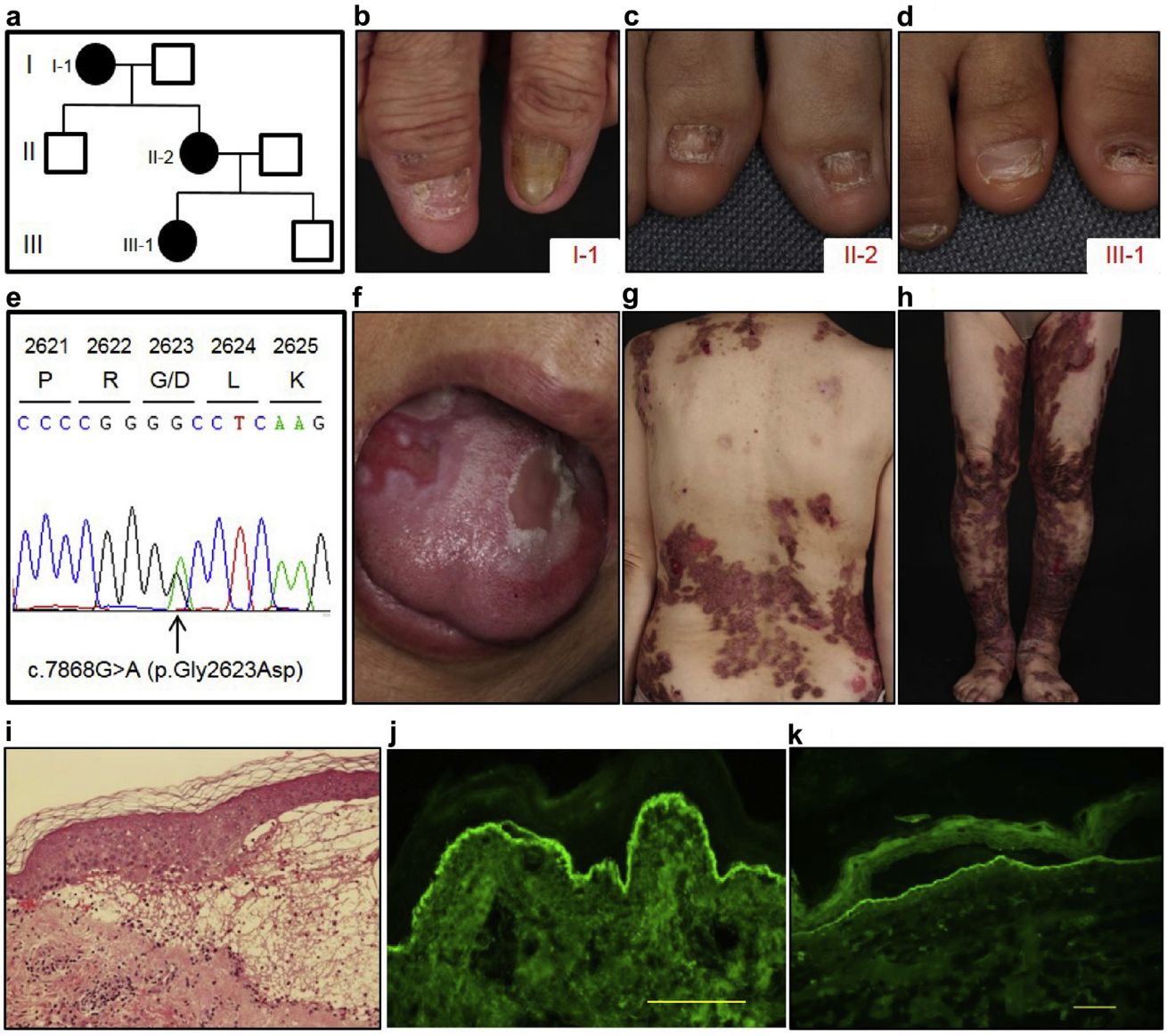

Figure 1. Clinical features of a Japanese family with dominant dystrophic epidermolysis bullosa (DDEB), in which one patient developed an autoimmune blistering disease. (**a**) Pedigree of the family. The affected individuals are colored in black. (**b**–**d**) Clinical features of the family members with DDEB. (**e**) Identification of a heterozygous missense mutation c.7868G>A (p.Gly2623Asp) in the *COL7A1* gene of the affected family members. (**f**–**h**) Clinical features of patient I-1 at age 63. She exhibited blistering formations on the oral mucosa (**f**) and all over her body (**g, h**) with scars and erosions. (**i**) Hematoxylin and eosin staining of a skin biopsy from patient I-1. Magnification: ×200. (**j**) Direct immunofluorescence with skin sections from patient I-1. (**k**) Indirect immunofluorescence using 1 M NaCl split normal human skin sections and serum from patient I-1. Scale bars = 100 μm (**j**), 50 μm (**k**).

332; this finding excluded the possibility of mucous membrane pemphigoid (Figure 2b). We also confirmed that COL7 protein was expressed in the patient's skin, although the expression looked slightly weaker than that in normal human skin (Supplementary Figure S1 online). To determine the domain of epitopes for the anti-COL7 auto-antibodies circulating in this patient, we overexpressed either the NC1 domain or the remaining domains of COL7 with a Flag tag in HEK293T cells, purified them with an anti-Flag antibody (Figure 2c), and performed Western blot using sera from the patient or a healthy control individual (Figure 2d); this analysis revealed that the patient's serum specifically reacted with the NC1 domain of COL7 (Figure 2d). Furthermore, a reactive oxygen species production assay showed that the patient's serum significantly activated normal human neutrophils (Figure 2e). On the basis of these results, we concluded that the auto-antibodies against the NC1 domain of COL7 caused EBA in the patient. For the treatment of EBA, administration of oral prednisolone (0.5 mg/kg daily) was started; however, the efficacy of this treatment was limited. The patient showed severe hypoalbuminemia and anemia; she ultimately died at the age of 66.

In this report, we present a female Japanese patient who had symptomatic, congenital DDEB as a child and developed EBA later in her life. The *COL7A1* mutation identified in the patient was a glycine substitution within the central triple helical domain of COL7, and the mutant COL7 protein was predicted to moderately inhibit triple helix formation of wild-type

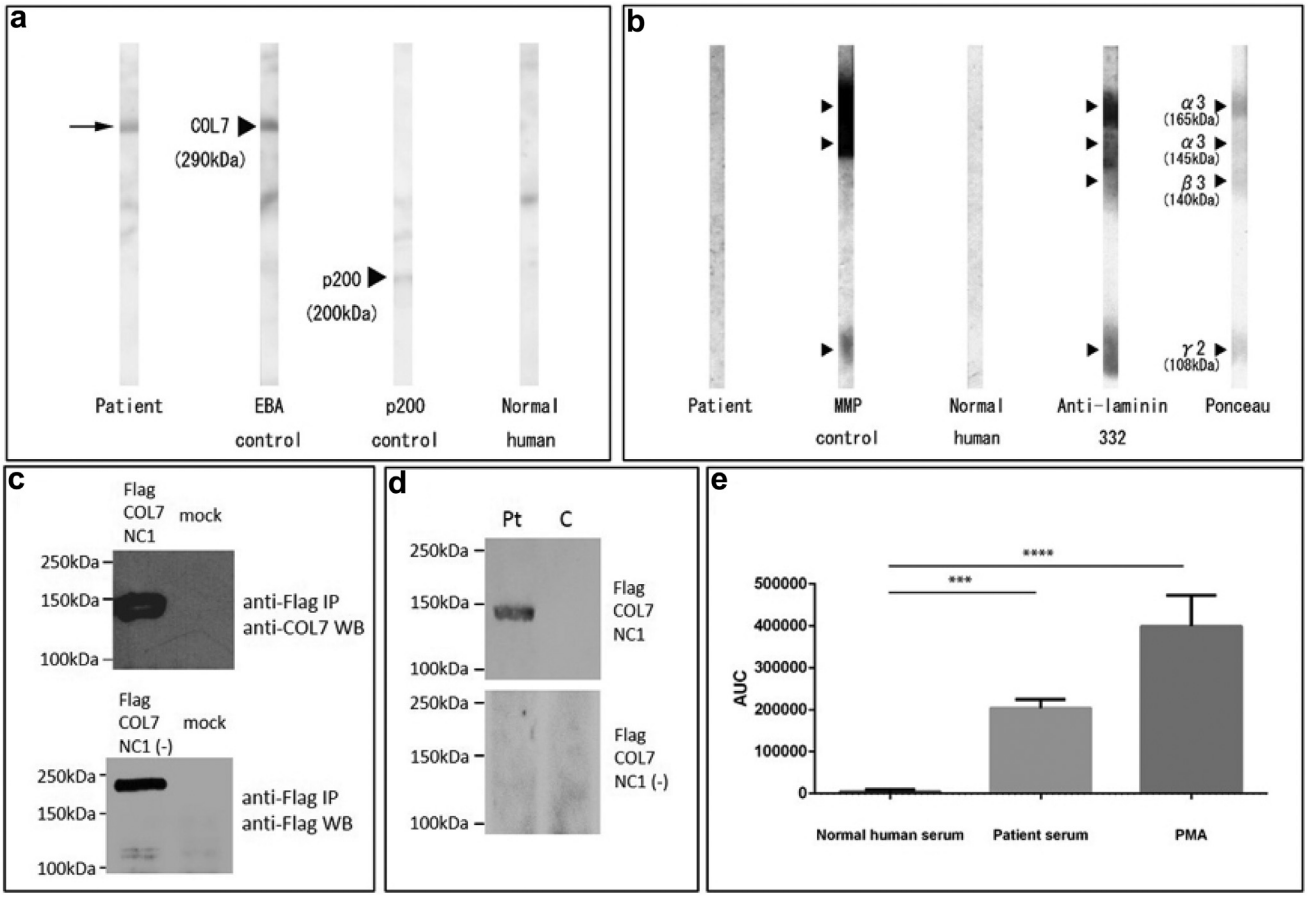

Figure 2. Detection of auto-antibodies against the NC1 domain of collagen VII (COL7). (**a**) Western blots (WB) using dermal extracts. Serum from patient I-1 recognized a 290 kDa fragment (lane 1; arrow), as did serum from a different patient with epidermolysis bullosa aquisita (EBA) (lane 2; arrowhead). Serum of a patient with anti-p200 pemphigoid showed a 200 kDa fragment (lane 3; arrowhead). (**b**) WB using purified laminin 332. Positive fragments are indicated by arrowheads. MMP, mucous membrane pemphigoid. (**c**) Flag-tagged COL7 proteins (Flag-COL7-NC1 and Flag-COL7-NC1 (−)) were purified by immunoprecipitation (IP), and were verified by WB. (**d**) WB with sera from patient I-1 (Pt) or a healthy control individual (C). **(e)** Reactive oxygen species (ROS) production by neutrophils was stimulated by incubation of the patient's serum with human COL7; phorbor myristate acetate (PMA) was used as positive control.

COL7 in a dominant-negative manner; this effect presumably resulted in aberrant anchoring fibrils and caused a mild form of DDEB (Figure 1b–d). Because previously reported cases of patients with RDEB with circulating anti-COL7 antibodies were not complicated by EBA (Pendaries et al., 2010; Tampoia et al., 2013; Woodley et al., 2014), not only the *COL7A1* mutation but also genetic modifiers and/or environmental factors might be involved in pathogenesis of EBA in our patient.

To date, only one case of DEB pruriginosa has been reported to have circulating anti-COL7 antibodies and cause EBA, whereas neither direct immunofluorescence nor indirect immunofluorescence showed IgG deposition at the DEJ (Jedlickova et al., 2012). Therefore, our findings provided more reliable evidence that anti-COL7 auto-antibodies generated in a patient with DDEB could induce EBA; they also indicated that *COL7A1* mutations may be a risk factor of EBA in some cases. Nevertheless, the exact mechanisms responsible for EBA development in DDEB and establishment of ideal treatments for such a rare condition await further studies.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1038/JID.2015.370.

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Validity of Self-Reported Psoriasis in a General Population: The HUNT Study, Norway

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TO THE EDITOR

A high prevalence of psoriasis has been reported in Norway, ranging from 4.8% to 11.8% (Bo et al., 2008; Danielsen et al., 2013; Kavli et al., 1985; Parisi et al., 2013). Prevalence estimates depend crucially on the validity of questionnaires (Jagou et al., 2006; Kurd and Gelfand, 2009; Lima et al., 2013; Plunkett et al., 1999; Rea et al., 1976; Wolkenstein et al., 2009). We aimed to validate self-reported psoriasis in a large population-based study in Norway using clinical skin examination performed by dermatologists as the gold standard and also to estimate the validation-based prevalence of psoriasis in a general Norwegian population.

Among adult participants of the third survey of the Nord-Trøndelag Health Study (HUNT3, 2006–8) (Krokstad et al., 2013), we invited random samples of 150 with and 700 without self-reported psoriasis, of whom 110 and 434 participated in the validation study, respectively (see Supplementary Figure S1 online). Validation was done by comparing the result of the self-reported question "Have you had or do you have psoriasis?" in HUNT3 to the outcome of the clinical interview and extensive skin examination performed by three dermatologists (EHM, IS, and MS). Because the diagnosis is based on clinical signs and symptoms (Boehncke and Schon, 2015), psoriasis was defined as having a positive history in combination with clinical findings present at the day of skin examination. In cases of complete remission on examination day, diagnostic confirmation had to be obtained either from a previous medical record collected from a dermatological clinic or by a former skin biopsy. To obtain estimates representative for the total HUNT3 population, appropriate weights were applied to account for differences in sampling probability. An age-standardized prevalence estimate according to the European standard population distribution for adults > 20 years was calculated (Pace et al., 2013) (see Supplementary Materials and Methods online).

General characteristics of the 544 participants did not differ substantially from the total HUNT3 study population or from the nonresponders (see Supplementary Tables S1 and S2 online). Compared with all people with self-report of psoriasis in HUNT3, participants in the validation study reported essentially similar characteristics of their psoriasis but slightly more often nail changes, psoriasis arthritis, and having the diagnosis confirmed by a dermatologist (see Supplementary Table S3 online).

The overall self-reported prevalence of psoriasis in HUNT3 was 5.8% (95% confidence interval [CI], 5.6–6.0%), and the validated prevalence was estimated to 8.0% (95% CI, 6.4–9.9%) (Table 1). Self-reported psoriasis had an estimated sensitivity of 56% (95% CI, 44–68%), a specificity of 99% (95% CI, 98–99%), a positive predictive value of 78% (95% CI, 69–85%), and a negative predictive value of 96% (95% CI, 94–98%) (Table 2). The positive predictive value increased to 84% if the psoriasis question was combined with the additional question, "Have you been diagnosed with psoriasis by a dermatologist?"

Four participants diagnosed with psoriasis in the period between the HUNT3 and the validation study were classified as true negatives. True-positive participants ($n = 86$) had a mean psoriasis area and severity index of 2.9, whereas false-negative participants ($n = 16$) had a mean psoriasis area and severity index of 0.9. Among false-negative participants, most had scalp psoriasis only ($n = 12$). The group of false positives ($n = 24$) consisted of subjects whose history of psoriasis could not be verified by a dermatologist or pathologist ($n = 10$); people with unspecified dermatitis ($n = 5$), benign skin tumors ($n = 2$), and urticaria ($n = 1$); and 6 individuals without any history of psoriasis or other relevant

Abbreviation: HUNT study, Nord-Trøndelag Health study

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